UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/773,792	02/06/2004	Thomas W. Dubensky JR.	ANZ-1200-UT2	8458

35938 7590 10/10/2008

Biotechnology Law Group
c/o Portfolioip
P.O. Box 52050
Minneapolis, MN 55402

EXAMINER	
GRASER, JENNIFER E	
ART UNIT	PAPER NUMBER
1645	
MAIL DATE	DELIVERY MODE
10/10/2008	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/773,792	DUBENSKY ET AL.	
	Examiner	Art Unit	
	Jennifer E. Graser	1645	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *11 April 2008*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *22,38-41,62,70 and 76-110* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *22,38-41,62,70 and 76-110* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *4/11/0887/11/08*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Continued Examination Under 37 CFR 1.114

1. A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 4/11/08 has been entered.

Claims 22, 38-41, 62, 70, 76-110 are under examination.

It is noted that the species election directly applies to all new claims, e.g., species: a mutation in *actA* and *inlB*.

Claim Rejections - 35 USC § 112-2nd paragraph

2. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

3. Claims 22, 38-41, 62, 70, 76-110 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 22 is vague and indefinite because it is unclear what is encompassed by "defective with respect to internalin B" and "defective with respect to ActA". Are these gene mutations or deletions? The metes and bounds of the claim cannot be understood. Does the term 'defective' mean the internalin has been rendered completely inactive, partially inactive, etc.? While the specification can be used to

provide definitive support, the claims are not read in a vacuum. Rather, the claim must be definite and complete in and of itself. Limitations from the specification will not be read into the claims. The claims as they stand are incomplete and fail to provide adequate structural properties to allow for one to identify what is being claimed. The claim should provide any structural properties which would allow for one to identify the bacterium without ambiguity. See also enablement and written description rejections. Applicants arguments have been fully and carefully considered but they are not deemed persuasive in overcoming the rejection. The structure of the claim is entirely vague and indefinite. The broadly recited functions do not allow for one to ascertain the structure of the bacterium being claimed for patent protection. The claims fail to correlate in scope to the gene mutants which Applicants have described in the instant specification. There is no specific structural alteration recited in claim 22. It is suggested that claim 31 be incorporated into claim 22.

Claim 39 is vague and indefinite because it recites 'the antigen' but the claim does not make it clear whether or not this is a heterologous antigen, e.g., is the bacterium transformed with heterologous DNA or is this a homologous antigen being expressed? Clarification and/or correction is requested.

Claims 40 and 77 are vague and indefinite because they are drawn to treating/protecting against *any* disease by administering the bacterium of claim 22; however, claim 22 is a modified L.monocytogenes bacterium. There are no heterologous antigens disclosed in claim 22 so it appears the bacterium would only be

able to treat disease caused by L.monocytogenes. The claim should be amended as such. Clarification and or correction is requested.

Claim 76, 81 and 82 are vague and indefinite because it is drawn to treating /protecting against cancer or an infectious disease yet there are no heterologous antigens disclosed in claim 22 so it appears the bacterium would only be able to treat disease caused by L.monocytogenes. Clarification and or correction is requested.

Claim 91 is vague and indefinite because it is unclear what is encompassed by "defective with respect to internalin B" and "defective with respect to ActA". Are these gene mutations or deletions? The metes and bounds of the claim cannot be understood. Does the term 'defective' mean the internalin has been rendered completely inactive, partially inactive, etc.? While the specification can be used to provide definitive support, the claims are not read in a vacuum. Rather, the claim must be definite and complete in and of itself. Limitations from the specification will not be read into the claims. The claims as they stand are incomplete and fail to provide adequate structural properties to allow for one to identify what is being claimed. The claim should provide any structural properties which would allow for one to identify the bacterium without ambiguity. See also enablement and written description rejections. Applicants arguments have been fully and carefully considered but they are not deemed persuasive in overcoming the rejection. The structure of the claim is entirely vague and indefinite. The broadly recited functions do not allow for one to ascertain the structure of the bacterium being claimed for patent protection. The claims fail to correlate in scope to the gene mutants which Applicants have described in the instant specification.

There is no specific structural alteration recited in claim 91. It is suggested that claim 92 be incorporated into claim 91.

Claim 102 is vague and indefinite because it is unclear what is encompassed by "defective with respect to internalin B" and "defective with respect to ActA". Are these gene mutations or deletions? The metes and bounds of the claim cannot be understood. Does the term 'defective' mean the internalin has been rendered completely inactive, partially inactive, etc.? While the specification can be used to provide definitive support, the claims are not read in a vacuum. Rather, the claim must be definite and complete in and of itself. Limitations from the specification will not be read into the claims. The claims as they stand are incomplete and fail to provide adequate structural properties to allow for one to identify what is being claimed. The claim should provide any structural properties which would allow for one to identify the bacterium without ambiguity. See also enablement and written description rejections. Applicants arguments have been fully and carefully considered but they are not deemed persuasive in overcoming the rejection. The structure of the claim is entirely vague and indefinite. The broadly recited functions do not allow for one to ascertain the structure of the bacterium being claimed for patent protection. The claims fail to correlate in scope to the gene mutants which Applicants have described in the instant specification. There is no specific structural alteration recited in claim 102.

Claim 108 is vague and indefinite because it is unclear which disease the composition is providing protection against. Is the disease caused by Listeria

monocytogenes or is the disease related to the non-Listerial antigen or is the disease something else entirely? Clarification and correction is requested.

Double Patenting

4. The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. A nonstatutory obviousness-type double patenting rejection is appropriate where the conflicting claims are not identical, but at least one examined application claim is not patentably distinct from the reference claim(s) because the examined application claim is either anticipated by, or would have been obvious over, the reference claim(s). See, e.g., *In re Berg*, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) or 1.321(d) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent either is shown to be commonly owned with this application, or claims an invention made as a result of activities undertaken within the scope of a joint research agreement.

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

5. Claims 22, 38-41, 62, 70, 76-110 provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1-66, 69-72, 74-76, 88-93, 102-109, 11-116, 118-128 of copending Application No. 10/883,599. Although the conflicting claims are not identical, they are not patentably distinct from each other because the co-pending claims encompass any bacterium which has been attenuated for proliferation by reaction with a nucleic acid targeted compound that reacts with the nucleic acid. The phenotypes 'attenuated for entry into non-phagocytic cells and for cell-to-cell spread' are forms of proliferation and are, therefore, encompassed in the language of the claims from 10/883,599. Co-pending

claims 13 and 16 recite that the microbe is a bacterium, more specifically L.moncytogenes and co-pending claim 18 encompasses mutations in both the actA and inlB genes. Co-pending claims 113 and 120 recite the same tumor antigens as the heterologous antigens recited in instant claim 35. Both applications teach the use of these bacterium as vaccines. Accordingly, since the scope of the instant claims is encompassed by the Genus recited in 10/883,599 the scope of the claims are not patentably distinct.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

6. Claims 22, 38-41, 62, 70, 76-110 are provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 20, 21, 83-87, 97-107, 109-118, 128-138, 140-149 and 150-189 of copending Application No. 10/773,618. Although the conflicting claims are not identical, they are not patentably distinct from each other because the co-pending claims encompass methods which use any bacterium which has been attenuated for proliferation by reaction with a nucleic acid targeted compound that reacts with the nucleic acid (see instant claims 25 and 26). The phenotypes 'attenuated for entry into non-phagocytic cells and for cell-to-cell spread' are forms of proliferation and are, therefore, encompassed in the language of the claims from 10/883,599. Co-pending claims 13 and 16 recite that the microbe is a bacterium, more specifically L.moncytogenes and co-pending claim 18 encompasses mutations in both the actA and inlB genes. Co-pending claims 113 and 120 recite the same tumor antigens as the heterologous antigens recited in instant claim 35. Both

applications teach the use of these bacterium in methods inducing an immune response to antigen and methods for treating or preventing a disease in a host. Accordingly, since the scope of the instant claims is encompassed by the Genus recited in 10/773,618 the scope of the claims are not patentably distinct.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

Claim Rejections - 35 USC § 112-Enablement

7. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

8. Claims 22, 38-41, 62, 70, 76-110 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

The instant claims are broadly drawn to an isolated *Listeria* bacterium which is attenuated both for entry into non-phagocytic cells and for cell-to-cell spread (the elected Group mutations in both actA and inlB). The instant specification has taught a double mutant (mutations in both actA and inlB) which has been deposited with the ATCC as accession number PTA-5562. The instant specification has demonstrated that this mutant strain was eliminated very quickly in the liver as compared to other strains tested, even though it was given in the highest dose. The mutant was shown to

elicit an immune response in mice. However, the specification has not taught (through challenge experiments) that this bacterium may provide protection (vaccine) or prevent infections caused by Listeria. Treatement of Listeria *monocytogenes* infection has been enabled, but not prevention or protection. The specification has not shown that this deposited bacterium, or any other prophetic bacterium, can treat or prevent cancer or any infection disease. The standard for cancer treatment is extremely high and it is unpredicatable.

The claims are broadly drawn to obtaining attenuated Listeria bacteria by mutating variant nucleotide sequences from many different species of Listeria yet the specification has only taught mutation of the actA and inlB genes from *L.monoctyogenes*. The instant claims encompass mutations in control sequences, the coding sequence or in a gene that controls expression of inlB or actA. It is disclosed that the function of the mutated gene may be from 25-100% less than the protein produced from a non-mutated gene sequence. See page 28. The specification fails to teach which portions of the actA and inlB gene are necessary for entry into non-phagocytic cells or for cell-to-cell spread. Accordingly, the scope of the instant claims is not enabled.

The use of these numerous different bacterium to treat or prevent ***any*** infectious disease, e.g., parasitic, fungal, bacterial from any Genus/species, viral, etc., and or to treat or prevent cancer is ***highly*** unpredictable. There are no results or working examples, which are required in such highly unpredictable arts, that enable the scope of these method claims. Genentech Inc. v. Novo Nordisk A/S (CAFC) 42 USPQ2d 1001

clearly states: "Patent protection is granted in return for an enabling disclosure of an invention, not for vague intimations of general ideas that may or may not be workable. See Brenner v. Manson, 383 U.S. 519, 536, 148 USPQ 689, 696 (1966) (stating, in context of the utility requirement, that "a patent is not a hunting license. It is not a reward for the search, but compensation for its successful conclusion.") Tossing out the mere germ of an idea does not constitute enabling disclosure. While every aspect of a generic claim certainly need not have been carried out by an inventor, or exemplified in the specification, reasonable detail must be provided in order to enable members of the public to understand and carry out the invention."

Given the complexity of the art, the breadth of the claims, the number of potential mutations, and the lack of guidance provided by the applicant, the examiner finds that there is insufficient information in the specification to enable those skilled in the art to practice the claimed invention without undue experimentation. The specification does not provide evidence that one skilled in the art would know what modifications, and what regions of inlB and actA to target for modifications, in order to produce an attenuated bacterium with the desired phenotype. Applicant's demonstration in the instant Specification that a species of mutant cells may serve as an effective vaccine does not enable one skilled in the art to make mutations in any Listeria bacterium, in such a way as to not only attenuate the bacterium through the specific mutation of the inlB and actA, but to also decrease the biological activity in such a way that it is responsible for the resultant attenuated bacterial phenotype. Genentech Inc. v. Novo Nordisk A/S (CAFC) 42 USPQ2d 1001 clearly states: "Patent protection is granted in return for an

enabling disclosure of an invention, not for vague intimations of general ideas that may or may not be workable. See Brenner v. Manson, 383 U.S. 519, 536, 148 USPQ 689, 696 (1966) (stating, in context of the utility requirement, that "a patent is not a hunting license. It is not a reward for the search, but compensation for its successful conclusion.") Tossing out the mere germ of an idea does not constitute enabling disclosure. While every aspect of a generic claim certainly need not have been carried out by an inventor, or exemplified in the specification, reasonable detail must be provided in order to enable members of the public to understand and carry out the invention. Bowie et al was also cited for providing evidence that information gathered from groups of similar or related proteins may not be sufficient to show one skilled in the art where to make mutations in a molecule and to have confidence that the mutations will have the desired result (Bowie, pages 1308-1309). Given the complexity of the art, the breadth of the claims, the number of potential mutations, and the lack of guidance provided by the applicant, the examiner finds that there is insufficient information in the specification to enable those skilled in the art to practice the claimed invention without undue experimentation.

Response to Applicants' arguments:

Applicants argue that providing protection against disease does not require 100% protection. Applicants argue that their working examples demonstrate that ability of an *actAinlB* **double *deletion*** mutant strain of ***Listeria monocytogenes*** to induce an immune response against an antigen, treat tumors in an in vivo **mouse** model (not protection against cancer (any and all types) was not shown) is specifically taught in the

specification. This has been fully and carefully considered. Applicants' arguments are not commensurate in scope with the claimed invention which do not recite the description of a particular mutation. Additionally, the mouse model does not directly correlate to protection of cancer in humans. The reduction of tumors in mice does not correlate to protection against cancer, but shows treatment. The dependent claims encompass an ***extremely*** broad scope of diseases to be treated/prevented. The specification does not enable this scope of invention, which also includes treatment and protection methods against any infection disease, e.g., parasitic, viral, fungal, bacterial, etc., and any type of cancer in humans or other mammals. Applicants arguments address a specific bacterium, an *actAinlB* **double *deletion*** mutant strain of ***Listeria monocytogenes***, but the claims are not drawn to this bacterium or its use in the claimed methods.

Accordingly, the rejection stands.

Claim Rejections - 35 USC § 103

9. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

10. Claim 22, 31, 38, 39, 40, 62, 70, 77, 81, 83, and 89, are rejected under 35 U.S.C. 103(a) as being unpatentable over Appelberg et al (Infect. Immun. Feb. 2000. 68(2): 912-914).

Appelberg et al teach mutants of *Listeria monocytogenes* which are defective in cell invasion *and* cell-to-cell spread. They teach an isolated *Listeria monocytogenes* mutants which are defective in the ***actA*** gene, the *plcB* gene and the *inlA* and ***inlB*** genes. These mutant strains were shown to be less virulent than wild-type strains. See abstract. These mutants were injected into mice and the immune response was monitored. The term "vaccine" is an intended use only. A recitation of the intended use of the claimed invention must result in a structural difference between the claimed invention and the prior art in order to patentably distinguish the claimed invention from the prior art. If the prior art structure is capable of performing the intended use, then it meets the claim. A "physiologically acceptable carrier" reads on water and therefore would be inherent in the preparation of the mutants. The reference specifically recites that "it will be interesting to analyze the characteristics of double mutants defective in both the ActA and the internalin pathways". See paragraph bridging pages 913-914.

Although the reference does not specifically teach a mutant with mutations in both the ActA and internalin B pathways, it would have been prima facie obvious to one of ordinary skill in the art to generate such a mutant because Appelberg et al specifically recite that "it will be interesting to analyze the characteristics of double mutants defective in both the ActA and the internalin pathways" because they hypothesize that invasion of hepatocytes by an ActA mutant is mediated by the InlAB-induced internalization of the bacteria directly by the hepatocytes". It is disclosed that this is critical to the way in which the bacterium can cause severe infection. See paragraph bridging pages 913-914. Accordingly, one of ordinary skill in the art would have been

motivated to produce a mutant deficient in both ActA and inlB in order to find a way of treating such a virulent infection.

Response to Applicants' Arguments:

Applicants argue that the double mutant defective in both ActA and the internalin B pathways was found to have superior immunogenicity and a superior liver safety profile. Given the fact that the prior art at the time the invention was made teaches the function for both the interalin pathway and ActA gene, it would have been *prima facie* obvious for one of ordinary skill in the art to create such a double mutant since doing so would create a less infective/pathogenic microorganism. Appelberg et al specifically recite that "it will be interesting to analyze the characteristics of double mutants defective in both the ActA and the internalin pathways" because they hypothesize that invasion of hepatocytes by an ActA mutant is mediated by the InlAB-induced internalization of the bacteria directly by the hepatocytes". It is disclosed that this is critical to the way in which the bacterium can cause severe infection. See paragraph bridging pages 913-914. Accordingly, one of ordinary skill in the art would have been motivated to produce a mutant deficient in both ActA and inlB in order to find a way of treating such a virulent infection.

Correspondence regarding this application should be directed to Group Art Unit 1645. Papers related to this application may be submitted to Group 1600 by facsimile transmission. Papers should be faxed to Group 1600 via the PTO Fax Center located in Remsen. The faxing of such papers must conform with the notice published in the Official Gazette, 1096 OG 30 (November 15,1989). The Group 1645 Fax number is 571-273-8300 which is able to receive transmissions 24 hours/day, 7 days/week.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished

applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Jennifer E. Graser whose telephone number is (571) 272-0858. The examiner can normally be reached on Monday-Thursday from 8:00 AM-6:30 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Robert Mondesi, can be reached on (571) 272-0956.

Any inquiry of a general nature or relating to the status of this application should be directed to the Group receptionist whose telephone number is (571) 272-0500.

/Jennifer E. Graser/
Primary Examiner, Art Unit 1645

10/8/08